MEMORANDUM

Date: October 22, 2009

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application DR1-01476

Enclosed is a letter from Dr. Judith Shizuru of Stanford University, an applicant for funding under RFA 09-01, CIRM Disease Team Research Awards. This letter was not received at CIRM five working days prior to the October ICOC meeting, but we are forwarding it pursuant to the ICOC Policy Governing Extraordinary Petitions for ICOC Consideration of Applications for Funding.

I have reviewed the petition (referencing reviewer comments and the submitted application as necessary) in consultation with the CIRM scientific staff.

Dr. Shizuru addresses a statement from the review summary that indicates reviewers viewed the proposal as unfocused and lacked novelty. The applicant contends that their approach may represent a different philosophy that considers incremental novelty important. We agree that incremental advances are important but a key objective of this RFA was to identify projects that were not simply making incremental advances but rather will offer a significant advantage over other therapies in practice or in the development pipeline. The reviewer comments are directed at the applicant not demonstrating a substantial benefit of this approach and offering little that is new or different from existing therapies. The applicant also states that their proposal was deemed unfocused due to their choice of addressing two disease indications. It is important to clarify that reviewers were referring not just to the two indications, but also to the proposed studies in the application that were viewed as not relevant to an IND filing.

The applicant also claims that reviewers did not discuss the broader implications of the proposal, which may impact on the treatment of other autoimmune diseases. In fact the review summary states that the "potential broader significance for this proposal derives from the applicant's claim that success in developing non-morbid regimens to achieve stable HSC engraftment will be applicable to the treatment of other diseases that can benefit from bone marrow transplantation." Reviewers discussed this point and some agreed with this view, but others argued that specific diseases will require specific tailor-made therapies.

This response provides an overall assessment by CIRM staff, based on our careful review of each of the points raised by the applicant. A point-by-point response would require reference to

confidential or proprietary information. CIRM staff is prepared to provide that at the ICOC meeting, should a member so request.

The enclosed letter represents the views of its author(s). CIRM assumes no responsibility for its accuracy.

In addition, a copy of the CIRM Review Summary for this application is provided for reference.

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October 25, 2009

Chairman of the ICOC
President of CIRM
Chief Scientific Officer of CIRM
210 King Street
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Dear Officers of CIRM

Please find attached an extraordinary petition for our application entitled "Hematopoietic Stem Cell Transplants for Severe Combined Immune Deficiency and Systemic Sclerosis". On behalf of our entire disease team, we wish to express our deep appreciate for the extensive time and consideration that you, members of the Grant Working Group, ICOC and the CIRM staff have devoted to reviewing these applications.

Please do not hesitate to contact me with any questions.

Best regards,

Judith A. Shizuru, M.D., Ph.D.
Associate Professor of Medicine
Division of Blood and Marrow Transplantation

CIRM EXTRAORDINARY PETITION: HEMATOPOIETIC STEM CELL TRANSPLANTS FOR SEVERE COMBINED IMMUNE DEFICIENCY AND SYSTEMIC SCLEROSIS

This document is written as an extraordinary petition regarding the CIRM Grant Working Group's review of our application entitled "Hematopoietic Stem Cell Transplants for Severe Combined Immune Deficiency and Systemic Sclerosis". We are writing this petition because we believe there is an important philosophical point about the nature of the type of research that was specifically solicited for the CIRM disease teams, and frankly, we wish to stimulate this debate at multiple levels of CIRM. We also believe that some of the tactical elements of our proposal were misunderstood, and though this issue will be later addressed in this petition, it is of lesser importance.

In the review, our application was " judged to be unfocused and felt to lack novelty". We wish to address this latter point first because it is on this point that there exists a major philosophical difference between the reviewers and our team. Our disease team is dedicated to incremental novelty and innovation. It is incremental by design because our focus is on translation of research to patient care. This progression requires a step-by-step approach where opportunities to optimize manifest themselves alongside setbacks and verification of results is as important as conceptual breakthroughs. Translation of basic research to patient treatments requires experience, knowledge and creative thinking leveraged simultaneously and in parallel to create a series of victories that individually may not seem "novel" but in the aggregate result in clinical applications that result in diseases being cured sooner rather than later. We believe that in the aggregate, our studies will break new and fundamentally important ground for the translation of stem cell research to clinical reality. Furthermore we believe we are in alignment with CIRM as it is our understanding that the charter of these CIRM disease teams is to safely bring our extensive preclinical experience in animals to serve the needs of patients.

The unifying focus of our studies is to achieve safe and durable engraftment of purified blood stem cells (hereafter referred to as hematopoietic stem cells or HSCs) that can be applied to all patients that can benefit from this potentially curative therapy. Transplantation of pure HSC will eliminate the major complication of blood and marrow transplantation called graft-versus-host disease (GVHD) which results from contaminating cells present in the standard grafts currently used to treat patients. GVHD remains a significant problem for transplant patients causing 10-15% of deaths from a transplant. Our studies represent the logical leap to the next era of blood and marrow transplantation since purified HSC transplantations will liberate the field from this complication and permit a much wider range of donors to be used such that nearly every patient will have an available donor unlike the current situation wherein, depending upon the specific disease and ethnic background an appropriate donor may be found for 25%-80% of patients.

There are also a multitude of diseases that could benefit from pure HSC transplantations. These diseases include but are not limited to many forms of cancer, childhood genetic disorders (i.e., immune deficiencies, sickle cell anemia), autoimmune disorders (i.e., Type 1 diabetes mellitus, multiple sclerosis, systemic lupus erythematosus). Furthermore, engraftment of HSCs from a donor can permit permanent acceptance of an organ graft, such as a kidney, from the same donor, without the need for immune suppressive drugs – an effect called immune tolerance induction. The knowledge that engrafted HSC can prepare a recipient to accept tissues from the same donor means that a similar strategy to allow tissue acceptance without immune suppressive drugs can be applied to tissues derived from sources such as embryonic stem cells or induced pluripotent stem cells generated from non-genetically identical donors. The implications of our studies extend well beyond the protocols proposed in the application and establish a fundamental platform for regenerative medicine and cellular therapy in general. Thus, what might be perceived as incremental gain by achieving robust HSC engraftment in the patient populations targeted in our proposal is in reality a direct and major step in the utilization

of HSC therapy for organ tolerance induction. We point out that these broader implications of the proposal were not discussed in the review.

The studies proposed in the application are built on a foundation of >10 years experience by members of the team who have pioneered the development of innovative ways to treat patients so that they will accept donor blood and marrow cell grafts with significantly reduced toxicity. The proposed work takes this foundation of translating research to clinical application to the next level and promises to have dramatic positive implications to the patient population. The next level is transplantation of pure human allogeneic HSCs and it has never been attempted. As one aspect of our current study, we proposed the use of a new and very promising antibody reagent to prepare patients for transplant. The comment from the review that "Reviewers judged this aspect of the proposal to be innovative, but they perceived a lack of novelty regarding the remainder of the therapeutic strategy" was highly troubling to us. It indicates that the reviewers did not consider transplantation of pure HSCs novel enough to support, even though it has never been done and regardless of its potential impact on the cellular therapy field. Further, this statement suggests that the supportive work which our team had previously developed and will make the execution of these studies possible, were discounted since they were no longer novel because we had already proven them effective. If this is the standard that CIRM is going to set for these disease team proposals, it will effectively eliminate proposals that are generated from teams that have dedicated themselves through the years to building foundations of incremental innovations that will allow reliable translations to clinical practice. It effectively sets a standard that encourages dramatic scientific leaps that will most likely take decades to fully realize in the patient setting. Our team does not believe this is the standard that CIRM or the reviewers intended to set. However we believe that by defining "novelty" in such narrow terms and discounting prior histories of incremental novelty that such a standard will, by default, be set and the charter of application of stem cell therapies to the clinic will gradually be supplanted by the appeal of pure research. This is the philosophical difference that our design team wishes to call attention to and to ask for clarification from the CIRM as to its position.

The other major criticism that we wish to question is more tactical in nature. The reviewers "found the proposal to be unfocused, as it targets two rather different disease indications". The choice of the two diseases (severe combined immune deficiency [SCID] and systemic sclerosis ([SSc]) was purposeful. The unifying goal of the proposal is to realize the potential of HSC-based therapy in humans so that this powerful therapy can be opened for non-malignant disease indications. Because the major obstacle to this goal is the barrier to HSC engraftment which is substantially higher than the barrier to conventional blood and marrow grafts, the focus of the grant is to safely achieve durable engraftment of HSC. The application proposes a step-wise approach to transplant children afflicted with SCID who, because they have greatly impaired immunity, have a lowered barrier to HSC engraftment as compared to other prospective transplant patients. We will utilize the specific reagents and knowledge gained from successes in the SCID population to move the technology to the adult patients with SSc. The application lays out the specific details of the regimens that will prepare patients for transplant. The inclusion of both SCID and SSc studies in our proposal is in fact focused on HSC based therapy and this two-step approach is fundamental to achieving a cure for the spectrum of patients with non-malignant diseases as listed above.

Two other points in the review were of concern to us:

(1) As we described above, we claim that there are a broad scope of diseases treatable by HSC transplants, including the induction of tolerance to transplanted organs. Apparently, there was disagreement amongst the reviewers on this point. Some agreed with our claims, whereas others argued that "tailor-made therapies will be required" and our results "would not be

applicable to more common diseases". Further criticisms along these lines suggest that specific and "relevant" mouse models have yet to be tested.

It has been known for >50 years that allogeneic bone marrow transplantation has remarkable and profound effects on recipient immunity. Indeed, the Nobel Prize in Medicine was awarded in 1960 for these studies performed in mice. The ability of allogeneic bone marrow transplantations to cure a broad spectrum of autoimmune diseases in mice has been repeatedly shown since the 1970's. In three mouse models of autoimmune disease (Type 1 diabetes, multiple sclerosis, and systemic lupus erythematosus) we have demonstrated that HSC transplantations cure the mice of their disease. There have also been many case reports that humans are cured of their autoimmune disease by allogeneic marrow transplantations – albeit with risks of GVHD. Blood and marrow transplantations are the only proven cure for most children with SCID, but the current way these transplants are performed are imperfect and place these patients at risk for complications that can result in death. Thus, we assert that the weight of scientific and medical evidence show the idea that "tailor-made therapies will be required" is unsubstantiated.

(2) Our proposal to use HSC transplantation as curative therapy for SCID and SSc was judged as not highly clinically competitive because (i) "reviewers pointed out that gene therapy using autologous HSCs could become the standard of care for immune deficiencies such as SCID while this project would be underway"; and (ii) "Similarly, the field of SSc therapeutics is presently extremely active, and other interventions under current investigation enjoy a robust supportive scientific platform."

Both statements are without foundation. For the last 30 years allogeneic hematopoietic cell transplantation has cured many hundreds of children with SCID. In contrast, gene therapy has been reported to treat only a handful (<50) of SCID afflicted patients, and this complex field continues to be fraught with difficulties including the unintended outcome of inducing a leukemia-like disease because of the complication of insertional mutagenesis. Likewise, very limited therapeutic options exist for patients with SSc and there is no established cure. Halting the destructive pathology of this disease is what we seek in our proposal. Perhaps the most promising treatment for SSc are the trials of autologous hematopoietic cell transplantation which have been shown to benefit ~one-third of SSc patients long-term. We point out here that our trial for SSc as proposed in the application will include comparisons of an autologous and allogeneic transplant arm. Because pure HSC grafts will be used in both study arms, patients treated on the autologous arm will receive grafts superior to those provided in other existing clinical trials as the reinfused HSC are devoid of contaminating immune cells thought to be the cause of SSc.

Finally, we understand and respect the challenges of judging so many competitive applications. We can accept that there were proposals submitted that the CIRM Grant Working Groups concluded might have a more immediate impact on patients in need of therapeutic options. We accept this conclusion because our team is committed to improving the lives of all patients as quickly as possible. We believe that the CIRM is also aligned with this goal and for this mutual goal to be realized we believe that we all need to recognize that progress in the clinical arena must be made with purposeful steps. It is of course tempting to be drawn towards research that forges major new ground in our scientific understanding of a disease. However far too often the importance of incremental novelty is overlooked and discounted, and without support and recognition for this arduous work the major breakthroughs might never be implemented in clinical application. We understand that the reviewers have a difficult job in striking this balance and it is our goal to encourage a dialogue on this important balance so as to provide guidance to them as well as to the research community. On behalf of my team we respectfully submit this extraordinary petition with this intent in mind.

REVIEW REPORT FOR CIRM RFA 09-01: DISEASE TEAM AWARDS I

DR1-01476: Hematopoietic Stem Cell Transplants for Severe Combined Immune Deficiency and Systemic Sclerosis

Recommendation: Not recommended for funding
First Year Funds Requested: $5,972,888
Final Score:
Total CIRM Funds Requested: $19,676,665

Public Abstract (provided by applicant)

Blood stem cells, which reside in the bone marrow (BM) can generate every type of blood and immune cell. They are the only cells necessary to re-establish blood formation if the BM is wiped out by disease or by treatments such as radiation or chemotherapy, as is the case for people who undergo a BM transplant. BM transplants have been performed for >50 years as life-saving procedures for many illnesses. However, patients do not receive pure blood stem cells, and the procedure is considered high risk mainly because BM cells received from a donor contain a combination of blood stem cells plus other mature immune cells. These mature cells pose a conundrum to physicians because on the one hand, the donor's mature cells can be beneficial to the patient by assisting blood stem cells to take root and grow in the recipient as well as potentially helping battle tumors in cancer patients. However on the other hand, these mature donor cells can attack the recipient's tissues, perceiving them as foreign and causing a syndrome called graft-versus-host disease (GVHD). Unfortunately, 10-20% of patients that undergo a transplant die from the consequences of GVHD.

In the last decade technologies were developed to purify blood stem cells eliminating mature immune cells, thereby eliminating the danger of GVHD. However, transplant physicians remained hesitant to use such grafts because of concerns that purified stem cells without the accompanying immune cells would not take and grow in the recipient. Members of this team have therefore worked out new ways in mice that may be used on patients so that they will accept purified blood stem cell grafts without significant side effects. The reagents we will develop belong to a class of proteins called antibodies. The specialized antibodies we will use are biologic tools that allow us to both purify human stem cells, and eliminate blood stem cells in the recipient thereby clearing the BM for donor cells. We plan to adapt the technologies that have worked successfully in mice to treat two different disorders for whom BM transplant can be curative, but if performed by conventional methods is very high risk and can be fatal for the patient.

The disorders we aim to cure by this approach are the childhood disease called severe combined immune deficiency (SCID), and the other is an autoimmune disease called systemic sclerosis (SSc). Children born with SCID lack immune cells to fight infections and without treatment die within the first year of life. Patients with severe forms of SSc experience thickening and tightening of the skin, lung and gastrointestinal problems which ultimately results in death after several years of suffering. We intend for these studies to result in superior treatments for these diseases. Since blood stem cell transplants have the capability of curing many other childhood and autoimmune disease, the ultimate impact of our studies will potentially be on a much broader spectrum of diseases.

Statement of Benefit to California (provided by applicant)

In 2004 California citizens passed a historic proposition supporting research that could result in the use of stem cells to cure many diseases. As a result, public and private institutions in California have emerged as leaders in this field, and scientists are now well on the path to producing tissues from primitive embryonic stem cells (ESCs). As scientists learn to direct these cells to become the tissues needed to replace damaged or failing ones, the obstacle of a patient rejecting these new tissues is a problem that must be overcome. The studies proposed by this Team address this issue.

Tissues or organs are rejected because they come from donors who are genetically different. Similarly, tissues derived from ESCs will be genetically different from patients who need these tissues and therefore at risk for rejection. In order to prevent tissue rejection, patients that undergo transplants of organs (i.e, heart, kidney, lung) must remain life-long on medications to suppress their white blood cells from rejecting the grafts.

There is one group of transplant patients that are routinely taken off their immune suppressive drugs -- bone marrow transplant (BMT) patients. These patients undergo BMT to cure them of severe cancers or inherited blood diseases. However, they can be liberated from their immune suppressive drugs because donor blood forming stem cells that take root in their bodies make the white blood cells that decide which tissues are identified as "foreign" or "self". New white blood cells re-educate the recipient's immune system to accept donor tissues as self. Thus, a state of harmony called immune tolerance is achieved so that donor blood is made without difficulty, and, in theory, the recipient can accept transplanted organs from the marrow donor without need for immune suppression. A similar strategy can be adapted to induce immune tolerance to tissues derived from ESCs. Remarkably, BMT also has the capability to cure autoimmune diseases such as multiple sclerosis, juvenile diabetes and many others. The major obstacle to use BMT beyond the treatment cancers has been the dangers associated with the procedure.
This Team will take a crucial step to make BMT safer by transplanting only purified blood stem cells. The benefits of these potential advancements to our state are many. First and foremost is the health and well-being of all Californians who face the many diseases treatable by BMT. In addition, it is a simple fact that with every major scientific advancement come immediate economic benefits to the region that generated those advancements. These benefits can manifest in the form of academic donations from sources around the world, service industries that support the medical establishments that practice the procedures, and hi tech companies who receive their funding globally. This activity can all result in greater investment in California and continued job creation that has made California such a desirable place to live.

Review Summary
The primary objective of this proposal is to develop a strategy that will enhance the outcome of allogeneic hematopoietic stem cell (HSC) engraftment for the treatment of severe combined immunodeficiency (SCID) and systemic sclerosis (SSc), a severe autoimmune disease. To accomplish this goal, the applicant proposes to develop clinical grade monoclonal antibodies for two purposes. First, certain antibodies will be used to purify the donor HSC population from mobilized peripheral blood, thereby reducing the risk of graft versus host disease (GvHD). Second, an antibody that targets HSC will be used to open niche space in the recipient, thereby improving stable donor HSC engraftment. In conjunction with additional conditioning regimens that are already in clinical use, the approach will be tested in mouse models of SCID and SSc and will be complemented by pharmacokinetic and toxicity studies in large animal models. Additional proposed activities include the optimization of regimens currently used to enhance HSC engraftment, optimization of a newborn SCID screening assay to identify SCID patients soon after birth when treatment with HSC would be optimal, and development of a customized proteomic microarray for identifying new autoantigens in SSc patients. These studies will provide the rationale for the proposed treatment plan for patients with SCID and SSc in future years.

Overall, reviewers were not enthusiastic about this proposal. Although supported by an excellent team, they found the proposal to be unfocused, as it targets two rather different disease indications, it includes several projects irrelevant to achieving regulatory filings, and it lacks novelty. The project's one innovative aspect, the development of less toxic conditioning regimens based on recipient HSC ablation, was supported by some convincing data in mouse models, but the most relevant mouse model has yet to be tested. Based on these deficiencies, reviewers were unable to recommend this application for funding.

Reviewers agreed that there are definite unmet medical needs in the treatment of SCID and SSc and the significance of this proposal lies in providing alternatives and developing less toxic therapies of greater efficacy. The current treatment, allogeneic HSC transplantation, is associated with high risk of morbidity and mortality, and if one of the conditioning modalities proposed will be found to be effective and without marked toxicity, reviewers felt it could advance the current clinical outcome in SCID, but the potential advantage for SSc patients is highly speculative at this stage. The allogeneic stem cell transplantation experience for SSc treatment remains essentially anecdotal at this time with added complexity due to similarities between GvHD and SSc. Potential broader significance for this proposal derives from the applicant's claim that success in developing non-morbid regimens to achieve stable HSC engraftment will be applicable to the treatment of other diseases that can benefit from bone marrow transplantation. Some reviewers agreed with this view, but others argued that specific diseases require specific tailor-made therapies, and although the results of this project will be of great interest, they will not be immediately

applicable to other much more common diseases.

The rationale for using the anti-HSC antibody to provide less-intense conditioning is logical given that it targets a receptor known to be crucial in maintaining hematopoiesis. Reviewers judged this aspect of the proposal to be innovative, but they perceived a lack of novelty regarding the remainder of the therapeutic strategy. For instance, fast cell sorting of human HSC is already extensively and successfully used in clinical bone marrow transplants, and thus a major effort in this area is not justified, although some reviewers noted that the proposed HSC purification strategy has the potential to address problems associated with subclinical GvHD. Further, reviewers would have appreciated an explanation why the use of some of the proposed combinations of already existing treatments had not already been achieved in the clinic, and pointed out that much of what is being proposed has already been under investigation for several decades. Reviewers strongly criticized the proposal's lack of focus, the applicant pursues two separate disease targets that are only connected by the fact that they are both potentially curable by allogeneic HSC transplantation, but otherwise share little in terms of rationale and approach. Reviewers supported the rationale for targeting SCID with the proposed strategies, but judged the SSc portion of the proposal to be extraneous. Furthermore, several components of the proposal, such as SCID screening assays and SSc autoantigen discovery are valuable ideas in themselves but do not impact on a successful investigational new drug (IND) application. Thus, the overall plan was judged to be quite diffuse. With regard to clinical competitiveness, reviewers pointed out that gene therapy using autologous HSCs could become the standard of care for immune deficiencies such as SCID while this project would be underway. Similarly, the field of SSc therapeutics is presently extremely active, and other interventions under current investigation enjoy a robust supportive scientific platform.

The mouse models developed and validated over many years both in terms of normal HSC transplantation and in multiple immunodeficient mutant mice, were generally considered a strength of this proposal. Reviewers lauded solid preliminary data using these models, suggesting that a low dose of HSCs administered over an extended period of time may be superior to a single bolus injection. Similarly, the effectiveness of antibody-mediated recipient HSC ablation in improving donor HSC engraftment is supported by convincing data on mouse and human HSC in relevant mouse models, although the approach would have been strengthened with a plan for evaluating immune recovery and not just engraftment. One reviewer raised questions about the validity of the proposed mouse models, since they exhibit low levels of T cells, B cells, and natural killer cells and do not mimic the SCID patients who harbor non-functional B cells. The applicant proposes to interrogate this clinical paradigm in two additional mouse models in the first two years of the proposed study. However, in one of these models, the barrier to engraftment is likely mediated by natural killer cells and thus it was unclear how the recipient HSC ablation would help overcome immune barriers. The reviewers thought that the other proposed model is more appropriate as it is suited to address the pathophysiology observed in many human SCID patients. However, if these proposed studies prove unsuccessful, the entire rationale for developing the anti-HSC strategy for use in SCID will be questionable. Similar questions arose with regard to the preclinical data for SSc applications. Without more substantial mouse data from relevant models in the context of relevant treatment modalities, reviewers were unsure whether an IND application could be filed within four years. However, if studies are successful in such models, the timelines for the generation of proposed antibodies were considered reasonable.

Overall, the developmental component of the proposal is likely feasible and sufficiently mature, as many aspects of the plan are either in practice today or have been developed previously. Since allogeneic HSC transplant studies have been attempted in both SCID and SSc patients, there is a large database of medical knowledge to build upon in order to develop appropriate clinical trial designs. The plan to develop the antibody reagents is clearly set out and the steps have been well defined including design of large animal pharmacokinetic studies by a contract research organization, followed by purification schemes and process development. The principal investigator (PI) recognizes multiple interactions with the FDA will be needed to get both the purified HSCs and the conditioning anti-HSC antibody ready for use in clinical studies. However, the reviewers questioned the need for the development of Good Manufacturing Practice (GMP)-grade antibodies for HSC purification and suggested that the PI should discuss with the relevant commercial provider the possibility of obtaining their existing GMP-grade antibodies, saving substantial time and cost. Similarly, obtaining a license or other agreement for the conditioning antibody

would be a more straightforward approach and lower risk than novel development routes.

Although tangential to the goal of filing an IND, the developmental plan aimed at establishing newborn screening to identify SCID in California or defining the custom array of SSc-relevant antigens is well designed. A reviewer pointed out that it seems premature to develop a Californian state wide screening program prior to the results becoming available from two other states that have already established pilot screening programs.

Milestones were judged to be achievable but the timeframe may be very tight. The milestones are meaningful but lacked specific criteria that would be used to identify optimal approaches. For example, reviewers were unclear how the relative effectiveness of various treatments in the mouse models would be judged and what endpoints will be considered meaningful in the large animal studies.

The PI has extensive knowledge of HSC cell biology and transplantation, and is highly qualified to lead the proposed program. This leadership is proven in terms of track record and ability to deliver meaningful outcomes to patients. The two co-PIs offer crucial support and complementary strengths, and the whole leadership team is most suitable to direct the preclinical studies proposed. In addition, a large team of experienced investigators has been carefully assembled. Given the track record of working together it would seem that the team will be able to work efficiently towards its goals. Reasonable attention has been paid to conflict resolution and structuring of communications to ensure productivity and focus, and the composition of the external advisory board is impressive, involving many of the leaders of HSC transplantation in the United States. Reviewers felt that the proposed budget is excessive, justification is often lacking sufficient detail for evaluation, the necessity for certain equipment and consulting input was questioned, and duplicating efforts were noted. The collaborators, resources, and environment are exceptional and capable of supporting the proposed work. The proposed collaborations are essential to completing the projects; they are well secured via letters of intent, and there is no doubt regarding the commitment to this project by the two involved academic institutions and the considerable depth of resources available at each campus. The time allocations are appropriate for each of the team members and in particular the leadership.

In conclusion, although supportive of the assembled team, the reviewers did not recommend this application for funding since they judged it to be unfocused and felt that it lacked novelty.

The following scientific Grants Working Group members had a conflict of interest with this application:
Balber, Andrew; Storb, Rainer